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Attestation

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The attached documents are exact copies of the international patent application described on the following page, as originally filed.

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Den Haag, den
The Hague,
La Haye, le

20. 04. 2005

Der Präsident des Europäischen Patentamts
Im Auftrag
For the President of the European Patent Office
Le Président de l'Office européen des brevets
p.o.

Patentanmeldung Nr.
Patent application no.
Demande de brevet n°

PCT/EP 04/002493

Blatt 2 der Bescheinigung
Sheet 2 of the certificate
Page 2 de l'attestation

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Tetrahydropyridoindole derivatives

Field of the invention:

The present invention relates to novel tetrahydropyridoindole derivatives and their use as potent CRTH2 receptor antagonists in the treatment of prostaglandin mediated diseases, to pharmaceutical compositions containing these derivatives and to processes for their preparation. In particular, such derivatives may be used alone or in pharmaceutical compositions for the treatment of both chronic and acute allergic/immune disorders such as allergic asthma, rhinitis, chronic obstructive pulmonary disease (COPD), dermatitis, inflammatory bowel disease, rheumatoid arthritis, allergic nephritis, conjunctivitis, atopic dermatitis, bronchial asthma, food allergy, systemic mast cell disorders, anaphylactic shock, urticaria, eczema, itching, inflammation, ischemia-reperfusion injury, cerebrovascular disorders, pleuritis, ulcerative colitis, eosinophil-related diseases, such as Churg-Strauss syndrome and sinusitis, basophil-related diseases, such as basophilic leukemia and basophilic leukocytosis in humans and other mammals.

Background of the invention:

Prostaglandin D2 is a known agonist of the thromboxane A2 (TxA2) receptor, the PGD2 (DP) receptor and the recently identified G-protein-coupled "chemoattractant receptor-homologous molecule expressed on Th2 cells" (CRTH2).

The response to allergen exposure in a previously sensitized host results in a cascade effect involving numerous cell types and release of a number of cytokines, chemokines, and multiple mediators. Among these critical initiators are the cytokines interleukin (IL)-4, IL-13, and IL-5, which play critical roles in Th2 cell differentiation, immunoglobulin (Ig)E synthesis, mast cell growth and differentiation, upregulation of CD23 expression, and the

differentiation, recruitment, and activation of eosinophils. The stimulated release of the array of mediators, causes end-organ damage, including constriction and hyperresponsiveness, vascular permeability, edema, mucous secretion, and further inflammation.

Because of the number of responses targeted, corticosteroids have proven to be the most effective therapy. Rather than antagonizing these specific responses in a directed way, another approach is to alter the immune response, that is, to change the nature of the immunological response to allergen. CRTH2 is preferentially expressed on Th2 cells and is a chemoattractant receptor for PGD2 that mediates PGD2-dependent migration of blood Th2 cells. Chemoattractants are responsible for the recruitment of both Th2 cells and other effector cells of allergic inflammation, which can provide the conceptual basis for the development of new therapeutic strategies in allergic conditions.

So far, few compounds having CRTH2 antagonistic activity have been reported in the patent literature. Bayer AG claims the use of Ramatroban ((3R)-3-(4-fluorobenzenesulfonamido)-1,2,3,4-tetrahydrocarbazole-9-propionic acid) for the prophylaxis and treatment of allergic diseases, such as asthma, allergic rhinitis or allergic conjuvatitis (GB 2388540). Further, (2-tert.-butoxycarbonyl-1, 2, 3, 4-tetrahydro-pyrido[4,3-b]indol-5-yl)-acetic acid and (2-ethoxycarbonyl-1, 2, 3, 4-tetrahydro-pyrido[4,3-b]indol-5-yl)-acetic acid are disclosed by Kyle F. et *al* in two patent applications (US 5817756 and WO 9507294, respectively).

Furthermore, oral bioavailability of the Ramatroban and its ability to inhibit prostaglandin D2-induced eosinophil migration *in vitro* has been reported (*Journal of Pharmacology and Experimental Therapeutics*, **305(1)**, p.347-352 (2003)).

Description of the invention:

It has now been found that compounds of the present invention are CRTH2 receptor antagonists. These compounds are useful for the treatment of both chronic and acute allergic/immune disorders such as allergic asthma, rhinitis, chronic obstructive pulmonary disease (COPD), dermatitis, inflammatory bowel disease, rheumatoid arthritis, allergic

nephritis, conjunctivitis, atopic dermatitis, bronchial asthma, food allergy, systemic mast cell disorders, anaphylactic shock, urticaria, eczema, itching, inflammation, ischemia-reperfusion injury, cerebrovascular disorders, pleuritis, ulcerative colitis, eosinophil-related diseases, such as Churg-Strauss syndrome and sinusitis, basophil-related diseases, such as basophilic leukemia and basophilic leukocytosis.

The following paragraphs provide definitions of the various chemical moieties that make up the compounds according to the invention and are intended to apply uniformly throughout the specification and claims unless an otherwise expressly set out definition provides a broader definition.

The term "alkyl", alone or in combination with other groups, means a straight-chain or branched-chain alkyl group with 1-5 carbon atoms as for example methyl, ethyl, propyl, isopropyl, butyl, sec.-butyl, tert.-butyl, isobutyl and the isomeric pentyls. Preferred are groups with 1 to 3 carbon atoms. This alkyl group may optionally be substituted by one to three substituents selected from cyano, halogen, hydroxy, cycloalkyl, alkenyl, alkoxy, alkenyloxy, trifluoromethyl, trifluoromethoxy, amino or carboxy.

The term "alkyl carbonyl", alone or in combination with other groups, means a R-CO- group, wherein R is hydrogen or an alkyl group as above-defined, examples are formyl, acetyl, propionyl, butyryl, isobutyryl and the like.

The term "alkenyl carbonyl", alone or in combination with other groups, means a R'-CO- group wherein R' is a straight-chain or branched-chain alkenyl group with 2 to 5 carbon atoms, examples are acryl, methacryl, crotonoyl or dimethylacryl.

The term "alkylcarbamoyl", alone or in combination with other groups, means a R-CO-NH- group wherein R is an alkyl group as above-defined, examples are methylcarbamoyl,

ethylcarbamoyl, propylcarbamoyl, isopropylcarbamoyl, butylcarbamoyl and tert.-butylcarbamoyl and the like.

The term "alkoxy", alone or in combination with other groups, means a group of the Formula R-O- in which R is a C_1-C_5 alkyl group, examples are methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, isobutoxy, *sec*-butoxy and tert.-butoxy, preferably methoxy and ethoxy.

The term "aryl" means an aromatic carbocyclic group from 6 to 14 carbon atoms having a single ring or multiple condensed rings. Preferred aryl include phenyl or naphthyl which optionally carries one or more substituents, preferably one or two substituents, each independently selected from cyano, halogen, hydroxy, alkyl, alkenyl, alkoxy, alkenyloxy, cycloalkyl, aryl, heteroaryl, trifluoromethyl, trifluoromethoxy, amino or carboxy and the like.

The term "aryl-C_1-C_5-alkyl" means a C_1-C_5 alkyl group having an aryl substituent in which the aryl group is as above-defined.

The term "aryl carbonyl", alone or in combination with other groups, means a group of the Formula Ar-CO- in which Ar is an aryl group as above-defined, examples are phenyl-carbonyl or naphtyl-carbonyl.

The term "aryl-C_1-C_5-alkyl carbonyl" means a C_1-C_5-alkyl carbonyl group having an aryl substituent in which the aryl group is as above-defined.

The term "aryl-C_1-C_5-alkoxy carbonyl" means a C_1-C_5-alkoxy carbonyl group having an aryl substituent in which the aryl group is as above-defined.

The term "arylcarbamoyl", alone or in combination with other groups, means a group of the Formula Ar-CO-NH- in which Ar is an aryl group as above-defined.

The term "cycloalkyl", alone or in any combination, means a saturated cyclic hydrocarbon moiety containing 3-15 carbon atoms, optionally substituted with one or more groups, each individually and independently selected from alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonyl, alkylcarbonylalkyl, alkylcarbonyloxy, alkylendioxy, alkylsulfinyl, alkylsulfinylalkyl, alkylsulfonyl, alkylsulfonylalkyl, alkylthio, alkylthioalkyl, alkynyl, amino, aminoalkyl, aminocarbonyl, aminocarbonylalkyl, aryl, arylalkenyl, arylalkyloxy, arylalkyl, aryloxy, aryloxycarbonyl, aryloxycarbonylalkyl, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, arylsulfonylalkyl, arylthio, arylthioalkyl, carboxy, carboxyalkyl, cyano, cyanoalkyl, formyl, formylalkyl, halogen, haloalkoxy, haloalkyl, heterocyclyl, hydroxy, hydroxyalkyl, mercapto, nitro, and the like. Representative examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like. In polycyclic cycloalkyl groups one of the distal rings may be aromatic, e.g., 1-indanyl, 2-indanyl, tetrahydronaphthalene, and the like.

The term "cycloalkylcarbonyl" means a carbonyl group having a cycloalkyl substituent in which the cycloalkyl group is as above-defined.

The term "cycloalkyl-C_1-C_5-alkyl-carbonyl" means C_1-C_5-alkyl-carbonyl group having a cycloalkyl substituent in which the cycloalkyl group is as above-defined.

The term "cycloalkyl-C_1-C_5-alkoxy-carbonyl" means C_1-C_5-alkoxy-carbonyl group having a cycloalkyl substituent in which the cycloalkyl group is as above-defined.

The term "heteroaryl" means a monocyclic heteroaromatic, or a bicyclic or a tricyclic fused-ring heteroaromatic group. Particular examples of heteroaromatic groups include

pyridyl, pyrrolyl, furyl, thienyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadia-zolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl,1,3,4-triazinyl, 1,2,3-triazinyl, benzofuryl, [2,3-dihydro]benzofuryl, isobenzofuryl, benzothienyl, benzotriazolyl, isobenzothienyl, indolyl, isoindolyl, 3H-indolyl, benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxa-zolyl, quinolizinyl, quinazolinyl, phthalazinyl, quinoxalinyl, cinnolinyl, naphthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, quinolyl, isoquinolyl, tetrazolyl, purinyl, pteridinyl, carbazolyl, xanthenyl or benzoquinolyl. Preferred heteroaryl include thiophenyl, pyridinyl or furanyl which optionally carries one or more substituents, preferably one or two substituents, each independently selected from cyano, halogen, hydroxy, alkyl, alkenyl, alkoxy, alkenyloxy, cycloalkyl, aryl, heteroaryl, trifluoromethyl, trifluoromethoxy, amino or carboxy and the like.

The term "heteroaryl C_1-C_5-alkyl" means C_1-C_5-alkyl group having a heteroaryl substituent in which the heteroaryl group is as above-defined.

The term "heteroaryl carbonyl", alone or in combination with other groups, means a group of the Formula Het-CO- in which Het is a heteroaryl group as above-defined.

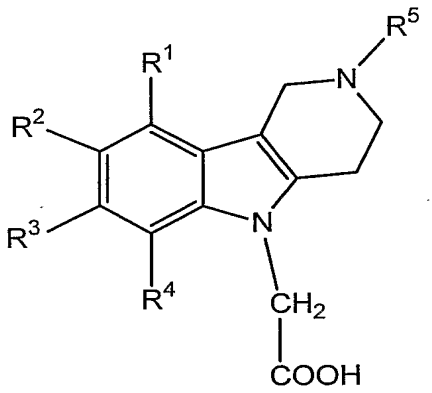
The term "heteroaryl-C_1-C_5-alkyl carbonyl" means a group of the Formula Het-C_1-C_5-alkyl-CO- in which Het is a heteroaryl group as above-defined.

The term "heteroaryl-C_1-C_5-alkoxy carbonyl" means a group of the Formula Het-C_1-C_5-alkoxy-CO- in which Het is a heteroaryl group as above-defined.

The expression "pharmaceutically acceptable salts" encompasses either salts with inorganic acids or organic acids like hydrochloric or hydrobromic acid, sulfuric acid, phosphoric acid, citric acid, formic acid, acetic acid, maleic acid, tartaric acid, benzoic acid, methanesulfonic acid, p-toluenesulfonic acid, and the like that are non-toxic to living organisms. In case the

compound of general Formula (I) is acidic in nature the expression encompasses salts with an inorganic base like an alkali or earth alkali base, e.g. sodium hydroxide, potassium hydroxide, calcium hydroxide, and the like which are also non-toxic to living organisms.

A first aspect of the present invention relates to novel tetrahydropyridoindole derivatives of the general Formula (I):



(I)

wherein

R^1, R^2, R^3 and R^4 independently represent hydrogen, C_1-C_5 alkyl, C_1-C_5 alkoxy, halogen, nitro, cyano or formyl;

R^5 represents alkyl carbonyl, alkenyl carbonyl, alkoxycarbonyl, alkyl, alkylcarbamoyl, aryl-C_1-C_5-alkyl, aryl carbonyl, aryl-C_1-C_5-alkyl carbonyl, aryl C_1-C_5-alkoxycarbonyl, arylcarbamoyl, cycloalkylcarbonyl, cycloalkyl-C_1-C_5-alkyl carbonyl, cycloalkyl-C_1-C_5-alkoxy carbonyl, heteroaryl C_1-C_5-alkyl, heteroaryl carbonyl, heteroaryl-C_1-C_5-alkyl carbonyl or heteroaryl C_1-C_5-alkoxycarbonyl;

with the proviso that when R^1, R^2, R^3 and R^4 represent hydrogen, R^5 is not an ethoxy-carbonyl group or a tert.-butoxycarbonyl group;

and optically pure enantiomers, mixtures of enantiomers, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixture of diastereoisomeric racemates, or meso forms and pharmaceutically acceptable salts thereof.

Preferred substituted tetrahydropyridoindole derivatives are those wherein R^1, R^2, R^3 and R^4 represent hydrogen.

In a preferred embodiment, R^1, R^2, R^3 and R^4 represent C_1-C_5 alkyl, C_1-C_3 alkoxy, halogen, nitro, cyano or formyl.

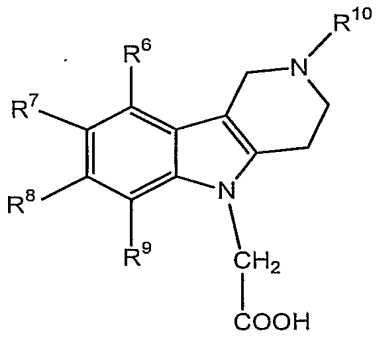
In another preferred embodiment one or two substituents selected from R^1, R^2, R^3 and R^4 represent methyl, trifluoromethyl, methoxy, fluoro, chloro or bromo.

In a particularly preferred embodiment, R^5 is selected from the group consisting of 2-cyclohexyl-2-phenyl-acetyl, 2-naphthalen-1-yl-acetyl, 2-naphthalen-2-yl-acetyl, 3-cyclopentyl-propionyl, 3-phenyl-propionyl, acetyl, diphenylacetyl, hexanoyl, (E)-but-2-enoyl, 9H-fluoren-9-ylmethoxycarbonyl, benzyloxycarbonyl, butoxycarbonyl, 3-phenyl-propyl, phenethyl, phenylacetyl, ethylcarbamoyl, 2-bromo-3-methyl-benzoyl, 2-bromo-5-methyl-benzoyl, 2-methoxy-benzoyl, 3,4,5-trimethoxy-benzoyl, 3,5-bis-trifluoromethyl-benzoyl, 3,5-dimethoxy-benzoyl, 3-chloro-benzoyl, 4-bromo-benzoyl, 4-chloro-benzoyl, 4-methoxy-benzoyl, 4-tert.-butyl-benzoyl, 4-trifluoromethoxy-benzoyl, 4-trifluoromethyl-benzoyl, or benzoyl; phenylcarbamoyl, 4'-ethyl-biphenyl-4-carbonyl, biphenyl-2-carbonyl, biphenyl-4-carbonyl, 2-ethoxy-naphthalene-1-carbonyl or naphthalene-1-carbonyl, cyclohexane-carbonyl, cyclopropane-carbonyl, pyridine-3-carbonyl, 2-chloro-6-methyl-pyridine-4-carbonyl, pyridine-4-carbonyl, furan-2-carbonyl, furan-3-carbonyl, 2-methyl-furan-3-carbonyl, 3-methyl-furan-2-carbonyl, 5-bromo-furan-2-carbonyl, pyrazine-2-carbonyl, benzo[b]thiophene-2-carbonyl, 5-chloro-thiophene-2-carbonyl, 3-methyl-thiophene-2-carbonyl, 5-methyl-thiophene-2-carbonyl, thiophene-2-carbonyl or thiophene-3-carbonyl.

A group of preferred compounds are those wherein R^1, R^2, R^3 and R^4 represent hydrogen, R^5 represents a C_1-C_5 alkoxycarbonyl group, an aryl-C_1-C_5-alkyl carbonyl group, an aryl carbonyl group or a heteroaryl carbonyl group.

Another group of preferred compounds are those wherein R^1, R^2, R^3 and R^4 represent H, R^5 represents a C_1-C_5 alkoxycarbonyl group, a phenyl C_1-C_5 alkyl carbonyl group, a naphthalene-1-carbonyl group or a thiophene-2-carbonyl group.

Another object of the invention relates to novel tetrahydropyridoindole derivatives of the following general Formula (II):



(II)

wherein

R^6, R^7, R^8 and R^9 independently represent hydrogen, C_1-C_5 alkyl, C_1-C_3 alkoxy or halogen;

R^{10} represents alkyl-carbonyl, alkoxy-carbonyl, alkenyl-carbonyl, C_3-C_6-cycloalkyl, C_3-C_6 cycloalkyl-carbonyl, C_3-C_6 cycloalkoxy-carbonyl, C_3-C_6 cycloalkyl-C_1-C_3-alkyl carbonyl, C_3-C_6 cycloalkyl-C_1-C_3-alkoxy carbonyl, phenyl-carbonyl, phenyl-C_1-C_3 alkyl carbonyl or phenyloxy-carbonyl whereby the phenyl group may be independently mono-, di- or tri-substituted with C_1-C_4 alkyl, C_1-C_3 alkoxy, halogen, trifluoromethyl or trifluoromethoxy, or mono-substituted with a phenyl group which in turn may be substituted with a C_1-C_3 alkyl or C_1-C_3-alkoxy group, naphtyl-carbonyl, fluorenyl-C_1-C_3-alkoxy-carbonyl, five- or six-

membered heteroaryl-carbonyl groups containing one to three heteroatoms consisting independently of oxygen, nitrogen or sulfur and which groups may be independently substituted with one or two C_1-C_3-alkyl, C_1-C_3-alkoxy, halogen or trifluoromethyl; with the proviso that when R^6, R^7, R^8 and R^9 represent hydrogen, R^{10} is not an ethoxy-carbonyl group or a tert.-butoxycarbonyl group;

and optically pure enantiomers, mixtures of enantiomers, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixture of diastereoisomeric racemates, or meso forms and pharmaceutically acceptable salts thereof.

Examples of preferred compounds are selected from the group consisting of:

(2-benzyloxycarbonyl-1, 2, 3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-acetic acid;

(2-butoxycarbonyl-1, 2, 3, 4-tetrahydro-pyrido[4,3-b]indol-5-yl)-acetic acid;

(2-9H-fluoren-9-ylmethoxycarbonyl-1, 2, 3, 4-tetrahydro-pyrido[4,3-b]indol-5-yl)-acetic acid;

(2-acetyl-1, 2, 3, 4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetic acid;

(2-phenylacetyl-1, 2, 3, 4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetic acid;

(2-benzoyl-1, 2, 3, 4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetic acid;

[2-(3,4,5-trimethoxy-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

(2-cyclohexanecarbonyl-1, 2, 3, 4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetic acid;

[2-(4-methoxy-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(thiophene-2-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(furan-2-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

(2-cyclopropanecarbonyl-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetic acid;

[2-(naphthalene-1-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(2-methoxy-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(4-trifluoromethyl-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(3,5-bis-trifluoromethyl-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(3-cyclopentyl-propionyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(3-phenyl-propionyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(biphenyl-4-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(4-tert.-butyl-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(4-trifluoromethoxy-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-((E)-but-2-enoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(4-chloro-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(3,5-dimethoxy-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

(2-diphenylacetyl-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetic acid;

(2-hexanoyl-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetic acid;

[2-(3-chloro-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(4-bromo-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(pyridine-3-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

(2-benzoyl-8-methoxy-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetic acid;

(2-benzoyl-7-methyl-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetic acid;

(2-benzoyl-8-bromo-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetic acid;

(2-benzoyl-8-methyl-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetic acid;

(2-benzoyl-6-methyl-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetic acid;

[2-(pyrazine-2-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(2-bromo-3-methyl-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(4'-ethyl-biphenyl-4-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(2-bromo-5-methyl-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(2-chloro-6-methyl-pyridine-4-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(biphenyl-2-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(5-bromo-furan-2-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(3-methyl-furan-2-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(2-methyl-furan-3-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(benzo[*b*]thiophene-2-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(5-chloro-thiophene-2-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(furan-3-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(2-naphthalen-2-yl-acetyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(thiophene-3-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(2-naphthalen-1-yl-acetyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

rac. [2-(2-cyclohexyl-2-phenyl-acetyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

(2-phenylcarbamoyl-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetic acid;

(2-ethylcarbamoyl-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetic acid;

sodium (2-phenethyl-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetate;

sodium [2-(3-phenyl-propyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetate;

[2-(2-ethoxy-naphthalene-1-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl]-acetic acid;

[2-(3-methyl-thiophene-2-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(5-methyl-thiophene-2-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(pyridine-4-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid.

Most preferred compounds according to Formula (I) are:

[2-(naphthalene-1-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(3-chloro-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(4'-ethyl-biphenyl-4-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(2-bromo-3-methyl-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

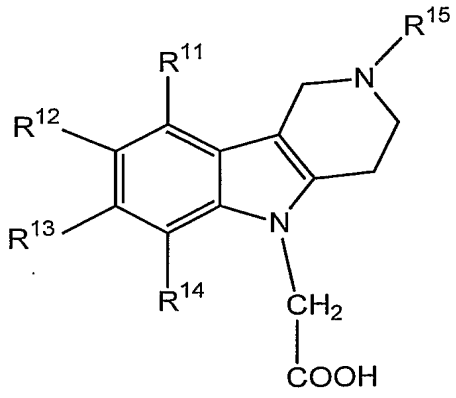
(2-benzoyl-8-bromo-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetic acid;

(2-benzoyl-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetic acid;

[2-(4-bromo-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl] acetic acid;

[2-(furan-2-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl] acetic acid.

A further object of the invention relates to a pharmaceutical composition containing at least one tetrahydropyridoindole derivative of the following general Formula (III):



(III)

wherein

R^{11}, R^{12}, R^{13} and R^{14} independently represent hydrogen, C_1-C_5 alkyl, C_1-C_5 alkoxy, halogen, nitro, cyano or formyl;

R^{15} represents alkyl carbonyl, alkenyl carbonyl, alkoxycarbonyl, alkyl, alkylcarbamoyl, aryl-C_1-C_5-alkyl, aryl carbonyl, aryl-C_1-C_5-alkyl carbonyl, aryl C_1-C_5-alkoxycarbonyl, arylcarbamoyl, cycloalkylcarbonyl, cycloalkyl-C_1-C_5-alkyl carbonyl, cycloalkyl-C_1-C_5-alkoxy carbonyl, heteroaryl C_1-C_5-alkyl, heteroaryl carbonyl, heteroaryl-C_1-C_5-alkyl carbonyl or heteroaryl C_1-C_5-alkoxycarbonyl;

and optically pure enantiomers, mixtures of enantiomers, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixture of diastereoisomeric racemates, or meso forms, pharmaceutically acceptable salts thereof and inert carrier materials or adjuvants.

Pharmaceutical composition containing at least one tetrahydropyridoindole derivative of the general Formula (III) is particularly useful for the prevention or treatment of diseases selected from the group consisting of both chronic and acute allergic/immune disorders such as allergic asthma, rhinitis, chronic obstructive pulmonary disease (COPD), dermatitis, inflammatory bowel disease, rheumatoid arthritis, allergic nephritis, conjunctivitis, atopic dermatitis, bronchial asthma, food allergy, systemic mast cell disorders, anaphylactic shock, urticaria, eczema, itching, inflammation, ischemia-reperfusion injury, cerebrovascular disorders, pleuritis, ulcerative colitis, eosinophil-related diseases, such as Churg-Strauss syndrome and sinusitis, basophil-related diseases, such as basophilic leukemia and basophilic leukocytosis

Another object of the present invention is a method for the treatment or prophylaxis of disease states mediated by CRTH2 comprising the administration to the patient of a pharmaceutically active amount of a tetrahydropyridoindole derivative according to Formula (III).

In a preferred embodiment of the invention, said amount is comprised between 1 mg and 1000 mg per day, particularly from 2 mg to 500 mg per day, more particularly from 5 mg to 200 mg per day.

Furthermore, the present invention also concerns a process for the preparation of a pharmaceutical composition comprising at least one tetrahydropyridoindole derivative according to general Formula (III) by mixing one or more active ingredients according to general Formula (III) with inert carrier materials or adjuvants in a manner known *per se*.

These pharmaceutical compositions can be administered enterally, such as orally (e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions), nasally (e.g. in the form of nasal sprays), rectally (e.g. in the form of suppositories) or dermally. However, the administration can also be effected parenterally, such as intramuscularly or intravenously (e.g. in the form of injection solutions).

Pharmaceutical compositions containing at least one compound of the general Formula (III) can be processed with pharmaceutically inert, inorganic or organic carrier materials and/or adjuvants for the production of tablets, coated tablets, dragées, and hard gelatine capsules. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts etc. can be used, for example, as such carrier materials or adjuvants for tablets, dragées, and hard gelatine capsules. Suitable carrier materials or adjuvants for soft gelatine capsules, are, for example, vegetable oils, waxes, fats, semi-solid substances and liquid polyols etc.

Suitable carrier materials or adjuvants for the production of solutions and syrups are, for example, water, polyols, saccharose, invert sugar, glucose etc. Suitable carrier materials or adjuvants for injection solutions are, for example, water, alcohols, polyols, glycerol, vegetable oils, etc. Suitable carrier materials or adjuvants for suppositories are, for example, natural or hardened oils, waxes, fats, semi-solid or liquid polyols, etc.

The above-described components for orally administered or injectable compositions are merely representative. Further materials as well as processing techniques and the like are set out in *Remington's Pharmaceutical Sciences*, 20th Edition, 2001, Marck Publishing Company, Easton, Pennsylvania, which is incorporated herein by reference.

These pharmaceutical compositions according to the invention can also be administered in sustained release forms or by using sustained release drug delivery systems.

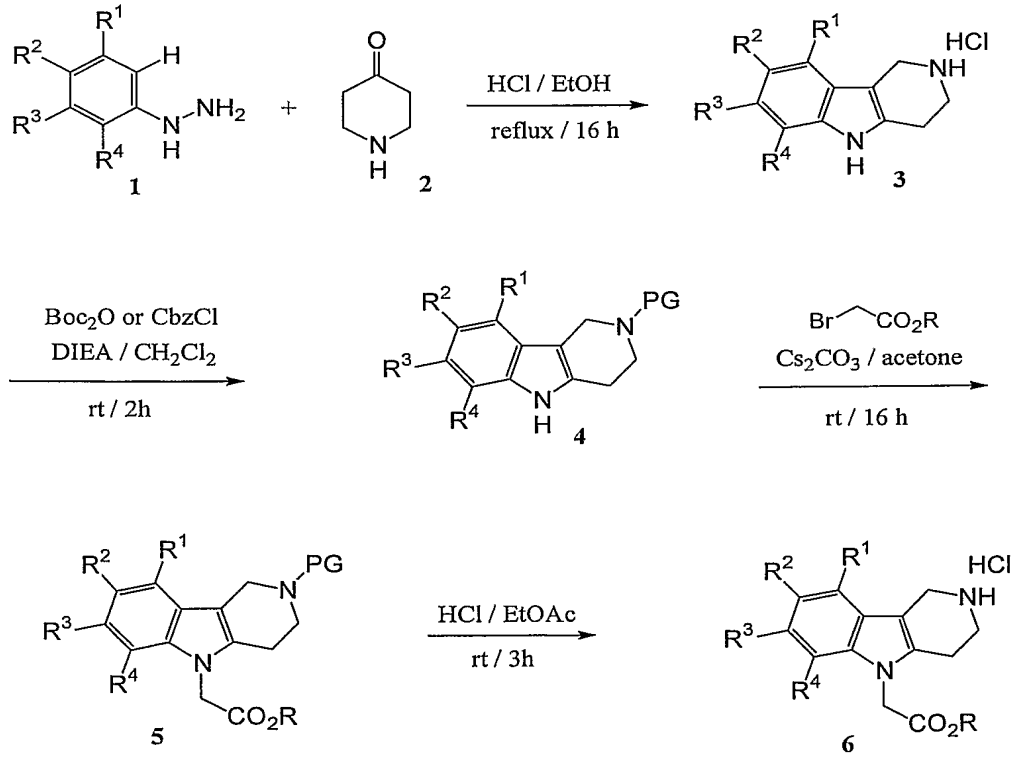
A further object of the invention is a process for preparing tetrahydropyridoindole derivatives according to Formulae (I) or (II). Compounds according to Formula (I) or (II) of the present invention are prepared according to the general sequence of reactions outlined in the schemes below, wherein R^1, R^2, R^3, R^4 and R^5 are as defined in Formula (I). The compounds obtained may also be converted into a pharmaceutically acceptable salt thereof in a manner known *per se*.

Compounds of the invention may be manufactured by the application or adaptation of known methods, by which is meant methods used hereinafter or described in the literature, for example those described by Larock R. C. in "*Comprehensive organic transformations: a guide to functional group preparations*", VCH publishers, (**1999**).

In the reactions described hereinafter, it may be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice, for example see Greene T. W. and Wuts P. G. M. in "*Protective groups in organic synthesis*" Wiley-Interscience (**1999**).

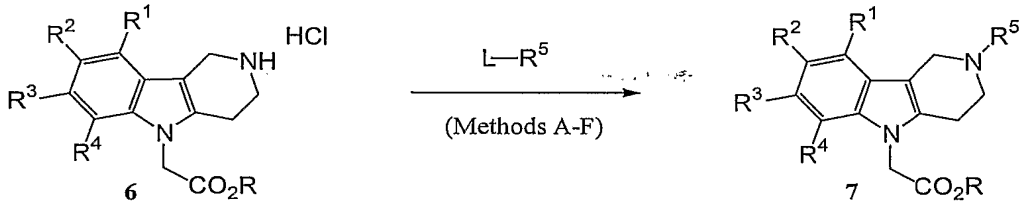
Generally, tetrahydropyridoindole derivatives of general Formula (I) are prepared as shown in Schemes 1 and 2, by condensing phenylhydrazine of Formula **1** and 4-piperidone monohydrate hydrochloride of Formula **2** in a Fischer indole synthesis to produce tetrahydropyridoindole of Formula **3**, using conditions known to a skilled person (e.g. M.

H. Block et al., *J. Med. Chem.* (**2002**), *45*, 3509-3523). The nitrogen atom in Formula **3** is protected with a protecting group (PG), such as alkoxycarbonyl, preferably tert.-butoxycarbonyl, or benzyloxycarbonyl, under standard conditions, affording a compound of Formula **4**. Then, compound of Formula **4** reacts with a compound of Formula L-CH_2CO_2R in which R is an alkyl group, preferably ethyl or tert.-butyl and L is a leaving group, in the presence of a base, such as caesium carbonate, sodium hydride, potassium tert.-butanolate or the like, in a suitable solvent, such as acetone, tetrahydrofuran or dioxane, to generate a compound of Formula **5**. Suitable L is a leaving group such as halo, in particular bromo or chloro; mesyloxy or tosyloxy. Preferably, the compound of Formula L-CH_2CO_2R is ethyl bromo-acetate. Deprotection under standard conditions delivers an intermediate of Formula **6**.

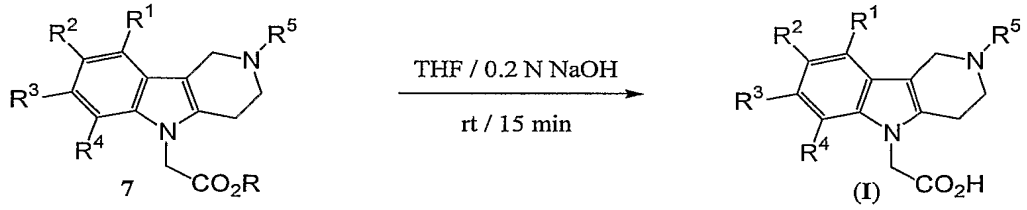


Scheme 1

Step a)



Step b)



Scheme 2

As illustrated in Scheme 2, intermediate of Formula **6** reacts in Step a) with a reagent of Formula L-R^5, where R^5 is as defined in Formula (I) hereinabove and L is a leaving group, such as hydroxy, or halo, in particular chloro or bromo. R^5 transferring reagent of Formula L-R^5 may be a chloroformate (**Method A**); or an acyl halide, preferably an acid chloride, or bromide, used as such (**Method B**); or generated *in situ* from the corresponding acid with a halogenating reagent under conditions known to a skilled person, preferably by means of oxalyl chloride or phosphorous oxychloride (**Method C**); or an acyl anhydride, transferring R^5 in the presence of a base, such as triethylamine, N,N-diisopropylethylamine, N-ethyl-morpholine, N-methylpiperidine, or pyridine, in a suitable solvent, such as dichloro-methane, tetrahydrofurane, or N,N-dimethylformamide, to give a product of Formula **7**.

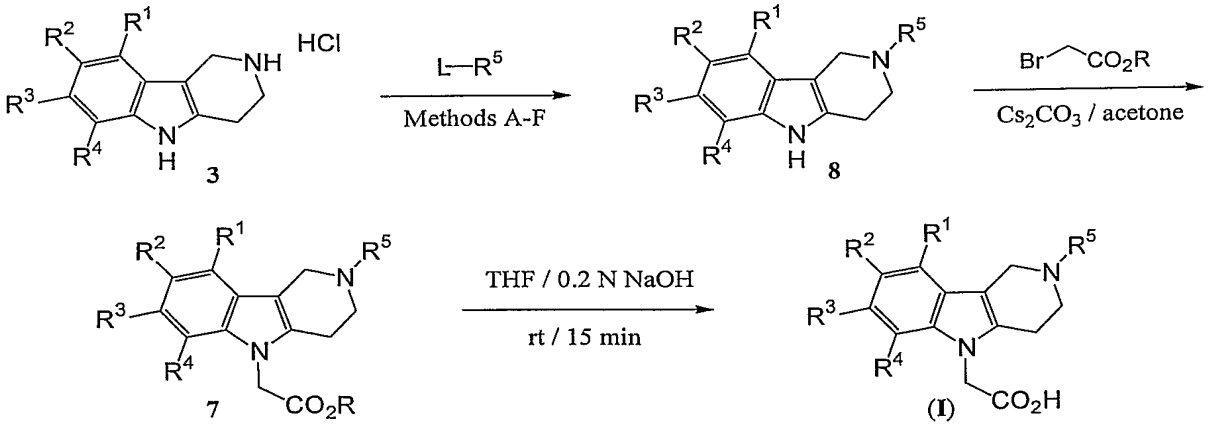
In another aspect, a carboxylic acid is used in the presence of a coupling reagent (**Method D**), such as 1,3-dicyclohexylcarbodiimide, diisopropylcarbodiimid, O-(7-azabenzotriazol-1-

yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate and the like, in the presence of a base described hereinabove, to give an amide of Formula 7.

In a further aspect, isocyanates or isothiocyanates (**Method E**), or alkylhalides (**Method F**) are used in the presence of a base to form products of Formula 7.

Hydrolysis of the ester group R in Formula 7 can be carried out using routine procedures, as outlined in Scheme 2, Step b), for example by stirring with aqueous sodium hydroxide, or trifluoroacetic acid to give a compound of Formula (I).

Alternatively, tetrahydropyridoindoles of Formula (I) can be synthesized in three consecutive steps as outlined in Scheme 3, starting from abovementioned Fischer indole product of Formula **3**, which is reacted first in a substitution reaction with abovementioned reagent of Formula L-R^5, using conditions as described in **Methods A** to **F**, to give a compound of Formula **8**. Subsequent alkylation of the indole nitrogen can be performed with a compound of the abovementioned Formula L-CH_2CO_2R, in which R and L is as defined above, under conditions as described in Scheme 1 for the alkylation of compound of Formula **4**, to give a precursor of Formula **7**. Final deprotection under standard conditions, as outlined in Scheme 2, Step b) delivers a compound of general Formula (I).



Scheme 3

In the following the present invention shall be illustrated by means of examples, which are not construed to be viewed as limiting the scope of the invention.

Experimental section:

Abbreviations:

AcOH	acetic acid
BSA	Bovine Serum Albumine
CH_2Cl_2	dichloromethane
DIEA	N,N-diisopropylethylamine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
EDTA	ethylenediamine tetraacetic acid
Et_3N	Triethylamine
ETOAc	Ethyl Acetate
EtOH	Ethanol
FLIPR	Fluorescent Imaging Plate Reader
g	gram
h	hour
H_2O	water
HCl	hydrochloric acid
HBSS	Hank's Balanced Salt Solution
HEPES	4-(2-Hydroxyethyl)-piperazine-1-ethanesulfonic acid
HPLC	High Performance Liquid Chromatography
k	kilo
K_2CO_3	potassium carbonate
$KHSO_4$	potassium hydrogen sulfate
l	liter
LC	Liquid Chromatography
LDA	Lithium di-isopropyl amide
MeOH	Methanol

$MgCl_2$	magnesium chloride
$MgSO_4$	magnesium sulfate
μ	micro
m	milli
M	molar
Me	methyl
MeOH	methanol
min	minutes
mol	mole
ESI-MS	Electrospray Ionization Mass Spectroscopy
N	Normality of solution
$NaHCO_3$	sodium hydrogenocarbonate
NaN_3	sodium azide
Na_2CO_3	sodium carbonate
NaCl	sodium chloride
NaOH	sodium hydroxide
Na_2SO_4	sodium sulfate
NH_4OH	ammonium acetate
p.o	per os
PyBOP	Benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium-hexafluorophosphate
PBS	phosphate buffer saline
PGD_2	Prostaglandin D2
PMSF	phenyl methylsulfonyl fluoride
$POCl_3$	phosphorous oxychloride
tr	retention time
sat.	saturated
tlc	thin layer chromatography
THF	Tetrahydrofuran
Tris	tris-(hydroxymethyl)aminomethane buffer

Chemistry

General remarks:

Temperatures are indicated in degrees Celsius (°C). Unless otherwise indicated, the reactions take place at room temperature (rt).

In mixtures, relations of parts of solvent or eluent or reagent mixtures in liquid form are given as volume relations (v/v), unless indicated otherwise.

Analytical HPLC conditions as used in the Examples below:

- LC-1: Analytical HPLC on a Xterra™ MS C_{18} column (50 x 2.1 mm, 5µm, Waters): Linear gradient of water/ 0.06% formic acid (LC-1) and acetonitrile/ 0.06% formic acid (B) from 5% to 95% B over 6 min; flow rate 0.25 ml/min, detection at 215 nm.

- LC-2: Analytical HPLC on a GromSil MS C_{18} column (50 x 2.1 mm, 5µm, Waters): Linear gradient of water/ 0.06% formic acid (LC-1) and acetonitrile/ 0.06% formic acid (B) from 5% to 95% B over 6 min; flow rate 0.25 ml/min, detection at 215 nm.

Preparation of 1,2,3,4-tetrahydro-pyrido[4,3-*b*]indole (Intermediates of Formula 6):

Intermediate 1: Ethyl (1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetate hydrochloride

A solution of ethyl (2-tert.-butoxycarbonyl-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetate (8.45 g, 23.6 mmol) in ethyl acetate (80 ml) is treated with a solution of 3M HCl in ethyl acetate (39.3 ml). After stirring at room temperature for 3 h, the solvent is removed in vacuo and the residue azeotroped twice with toluene. The crude product is suspended in diethyl ether, filtered off, washed with diethyl ether and dried. Finally, pure title compound is obtained as beige solid (5.49 g) in 79% yield. t_R (LC-2) 1.41 min; ESI-MS (positive ion): *m/z* 259.33 $[M+H]^+$ (calcd 258.32 for $C_{15}H_{18}N_2O_2$).

1a) 2,3,4,5-Tetrahydro-1H-pyrido[4,3-*b*]indole hydrochloride:
4-Piperidone monohydrate hydrochloride (10 g, 65.1 mmol) and phenylhydrazine

hydrochloride (9.4 g, 65.1 mmol) are suspended in ethanol (200 ml) and stirred at reflux overnight. The resulting solid is filtered off and washed with diethyl ether to afford pure sub-title compound (11.9 g) in 88% yield. t_R (LC-2) 0.89; ESI-MS (positive ion): *m/z* 173.34 $[M+H]^+$ (calcd 172.23 for $C_{11}H_{12}N_2$).

1b) 2-tert.-Butoxycarbonyl-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indole:
A solution of di-tert.-butyl-dicarbonate (7.3 ml, 35.2 mmol) in dry dichloromethane (100 ml) is added to a mixture of 2,3,4,5-tetrahydro-1H-pyrido[4,3-*b*]indole hydrochloride (7.0g, 33.5 mmol) and DIEA (20 ml, 117 mmol) in dry dichloromethane (200 ml). After stirring at rt for 2 h, water (100 ml) and 2N aqueous $KHSO_4$ solution (60 ml) are added. The organic layer is separated and washed successively with water and brine, dried over Mg_2SO_4, filtered and evaporated, affording crude sub-title compound as yellow oil, which solidified upon standing and is used in the next step without further purification. t_R (LC-2) 2.31 min; ESI-MS (positive ion): *m/z* 295.37 $[M+Na]^+$ (calcd 272.34 for $C_{16}H_{20}N_2O_2$).

1c) Ethyl (2-tert.-butoxycarbonyl-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetate
To a stirred suspension of crude 2-tert.-butoxycarbonyl-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol (33.5 mmol) and caesium carbonate (25.1 g, 77.1 mmol) in dry acetone is added ethyl bromoacetate (5.6 ml, 50.3 mmol). The reaction mixture is stirred at rt overnight and then filtered over a small plug of Celite. The filtrate is concentrated under reduced pressure and the residue is purified by silica gel column chromatography (hexane/ EtOAc 5:1) to afford pure sub-title compound as yellow oil (8.45 g) in 70% yield (over two steps). t_R (LC-2) 2.46 min; ESI-MS (positive ion): *m/z* 381.54 $[M+Na]^+$ (calcd 358.43 for $C_{20}H_{26}N_2O_4$).

<u>Intermediate 2:</u> Ethyl (8-bromo-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetate hydrochloride

The title compound is prepared using a procedure analogous to Intermediate 1, substituting 4-bromophenylhydrazine for phenylhydrazine in Step 1a).

Intermediate 3: Ethyl (8-methyl-1,2,3,4 -tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetate hydrochloride

The title compound is prepared using a procedure analogous to Intermediate 1, substituting 4-methylphenylhydrazine for phenylhydrazine in Step 1a).

Intermediate 4: Ethyl (7-methyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-acetate hydrochloride

The title compound is prepared using a procedure analogous to Intermediate 1, substituting 3-methylphenylhydrazine for phenylhydrazine in Step 1a).

Intermediate 5: Ethyl (6-methyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-acetate hydrochloride

The title compound is prepared using a procedure analogous to Intermediate 1, substituting 2-methylphenylhydrazine for phenylhydrazine in Step 1a).

Example 1: (2-tert.-Butoxycarbonyl-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetic acid

A stirred solution of ethyl (2-tert.-butoxycarbonyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-acetate (15 mg, 0.039 mmol) in THF (0.6 ml) is treated with 0.2 N aqueous NaOH (0.29 ml, 0.058 mmol) at rt for 15 min. The reaction mixture is diluted with water (2 ml) and washed with diethyl ether (2 ml), then neutralized with conc. HCl (58 µl), and extracted with dichloromethane. The solvent is evaporated and the crude product is recrystallized from acetonitrile to afford pure compound as a yellow solid: t_R (LC-1) 2.16 min; ESI-MS (positive ion): *m/z* 353.32 $[M+Na]^+$ (calcd 330.38 for $C_{18}H_{22}N_2O_4$).

Example 2: (2-Benzyloxycarbonyl-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetic acid (Method A)

To a stirred solution of Intermediate 1 (29.5 mg, 0.10 mmol) and DIEA (51 µl, 0.30 mmol) in dichloromethane (1 ml) is added benzyl chloroformate (16 µl, 0.11 mmol). The reaction

mixture is stirred at rt for 1 h, 1N aqueous HCl (2 ml). The aqueous layer is extracted twice with dichloromethane. The combined organic layers are washed with water, saturated $NaHCO_3$ solution, then are concentrated to dryness to afford crude ethyl (2-benzyloxycarbonyl-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetate: t_R (LC-1) 2.52 min; ESI-MS (positive ion): *m/z* 393.19 $[M]^+$ (calcd 392.45 for $C_{23}H_{24}N_2O_4$).

The title compound is obtained using conditions for the hydrolysis of the above crude analogous to Example 1: t_R (LC-1) 2.22 min; ESI-MS (positive ion): *m/z* 387.14 $[M+Na]^+$ (calcd 364.40 for $C_{21}H_{20}N_2O_4$).

Examples 3-5 of the following Table 1 are prepared using a procedure analogous to that described for Example 2, substituting the appropriate chloroformates for benzyl chloroformate.

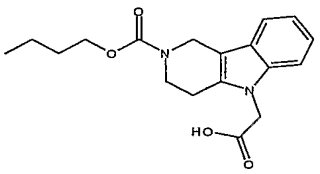
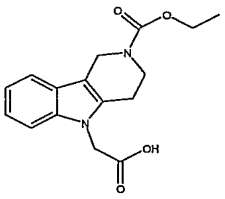
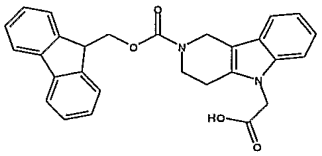
Ex.	Structure	Name	Mol Formula Mol Weight	t_R [min] (LC)	MS Data *m/z* $[M+H]^+$
3		(2-butoxycarbonyl-1,2,3,4-tetrahydro-pyrido[4,3-*b*]-indol-5-yl)-acetic acid	$C_{18}H_{22}N_2O_4$ 330.38	2.22 (LC-1)	331.22
4		(2-ethoxycarbonyl-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetic acid	$C_{16}H_{18}N_2O_4$ 302.33	1.95 (LC-1)	303.33
5		(2-9H-fluoren-9-ylmethoxycarbonyl-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetic acid	$C_{28}H_{24}N_2O_4$ 452.51	2.46 (LC-1)	453.21

Table 1

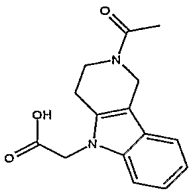
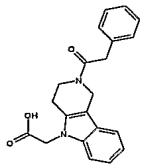
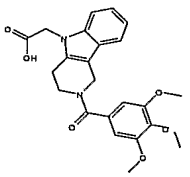
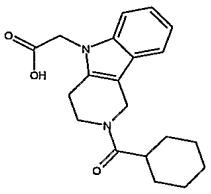
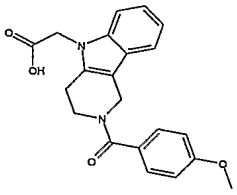
Example 6: [2-(Naphthalene-1-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid (Method B)

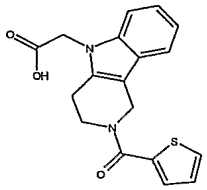
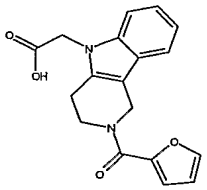
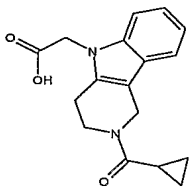
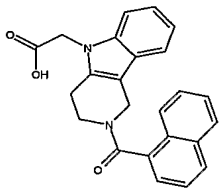
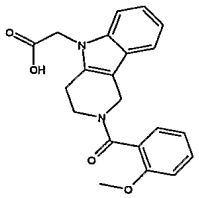
Step a): To a stirred solution of Intermediate 1 (ethyl (1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetate hydrochloride, 25.0 mg, 0.085 mmol) and DIEA (73 µl, 0.425 mmol) in dichloromethane (0.5 ml) is added benzoyl chloride (15 mg, 0.11 mmol). The resulting yellow solution was kept stirring at rt for 1h and then is quenched by adding saturated aqueous $NaHCO_3$ solution (2 ml). The organic layer is separated and washed with water (2

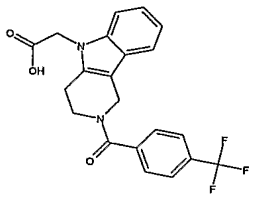
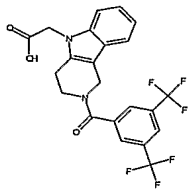
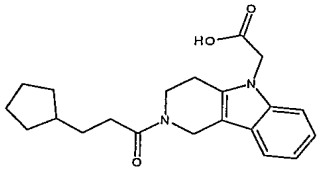
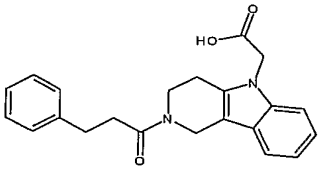
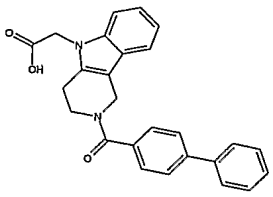
ml). After removal of the solvent, crude ethyl (2-benzoyl-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetate is obtained pure as a yellow glassy solid: t_R (LC-2) 2.20 min; ESI-MS (positive ion): *m/z* 386.31 $[M+Na]^+$(calcd 362.42 for $C_{22}H_{22}N2O_3$).

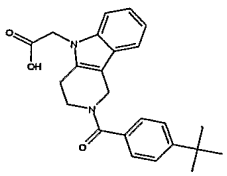
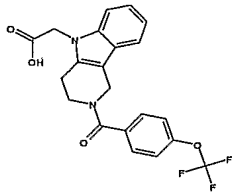
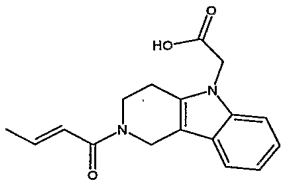
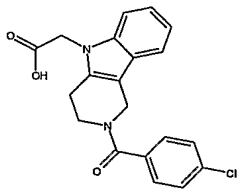
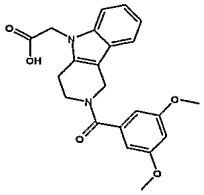
Step b): A solution of crude ethyl (2-benzoyl-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetate (0.085 mmol) in THF (0.5 ml) is treated with 0.2 N aqueous NaOH solution (0.64 ml) at rt for 15 min. Then, the yellow reaction mixture is diluted with water (2 ml), washed with diethyl ether (2 ml), acidified with conc. HCl to pH 1 and extracted with dichloromethane. The combined organic phases are washed with water, then dried over Na_2SO_4, filtered and the solvent evaporated. The crude product is recrystallized from diisopropyl ether to give pure title compound as yellow solid: t_R (LC-1) 2.95 min; ESI-MS (positive ion): *m/z* 335.17 $[M+H]^+$ (calcd 334.37 for $C_{20}H_{18}N_2O_3$).

Examples 7-31 of the following Table 2 are prepared using a procedure analogous to that described for Example 6, substituting the appropriate acid chloride for benzoylchloride and substituting the appropriate Intermediate for Intermediate 1.

Ex.	Structure	Name	Mol Formula Mol Weight	t_R [min] (LC)	MS Data *m/z* $[M+H]^+$
7		(2-acetyl-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetic acid	$C_{15}H_{16}N_2O_3$ 272.30	1.65 (LC-2)	273.21
8		(2-phenylacetyl-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetic acid	$C_{21}H_{20}N_2O_3$ 348.40	1.97 (LC-1)	349.37
9		[2-(3,4,5-trimethoxy-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid	$C_{23}H_{24}N_2O_6$ 424.45	1.92 (LC-1)	425.17
10		(2-cyclohexanecarbonyl-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetic acid	$C_{20}H_{24}N_2O_3$ 340.42	2.08 (LC-1)	341.22
11		[2-(4-methoxy-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid	$C_{21}H_{20}N_2O_4$ 364.40	1.96 (LC-1)	365.17

Ex	Structure	Name	Mol Formula Mol Weight	t_R [min] (LC)	MS Data *m/z* $[M+H]^+$
12		[2-(thiophene-2-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid	$C_{18}H_{16}N_2O_3S$ 340.40	1.94 (LC-1)	341.09
13		[2-(furan-2-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid	$C_{18}H_{16}N_2O_4$ 324.34	1.86 (LC-1)	325.11
14		(2-cyclopropanecarbonyl-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetic acid	$C_{17}H_{18}N_2O_3$ 298.34	1.82 (LC-1)	299.12
15		[2-(naphthalene-1-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid	$C_{24}H_{20}N_2O_3$ 384.43	2.09 (LC-1)	385.17
16		[2-(2-methoxy-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid	$C_{21}H_20N_2O_4$ 364.40	1.94 (LC-1)	365.17

Ex	Structure	Name	Mol Formula Mol Weight	t_R [min] (LC)	MS Data *m/z* $[M+H]^+$
17		[2-(4-trifluoromethyl-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid	$C_{21}H_{17}N_2O_3F_3$ 402.37	2.16 (LC-1)	403.13
18		[2-(3,5-bis-trifluoromethyl-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid	$C_{22}H_{16}N_2O_3F_6$ 470.37	2.34 (LC-1)	471.11
19		[2-(3-cyclopentyl-propionyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid	$C_{21}H_{26}N_2O_3$ 354.45	2.22 (LC-1)	355.17
20		[2-(3-phenyl-propionyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid	$C_{22}H_{22}N_2O_3$ 362.43	2.09 (LC-1)	363.19
21		[2-(biphenyl-4-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid	$C_{26}H_{22}N_2O_3$ 410.47	2.26 (LC-1)	411.16

Ex	Structure	Name	Mol Formula Mol Weight	t_R [min] (LC)	MS Data *m/z* $[M+H]^+$
22		[2-(4-tert.-butyl-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid	$C24H_{26}N_2O_3$ 390.48	2.29 (LC-1)	391.22
23		[2-(4-trifluoromethoxy-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid	$C21H1_7N_2O_4F_3$ 418.37	2.20 (LC-1)	419.06
24		[2-((E)-but-2-enoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid	$C_{17}H_{18}N_2O_3$ 298.34	1.82 (LC-1)	299.12
25		[2-(4-chloro-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid	$C_{20}H_{17}N_2O_3Cl$ 368.82	2.10 (LC-1)	369.12
26		[2-(3,5-dimethoxy-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid	$C_{22}H_{22}N2O5$ 394.43	2.01 (LC-1)	395.17

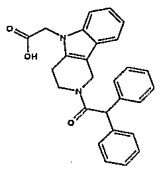
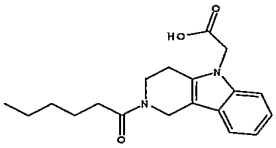
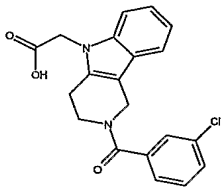
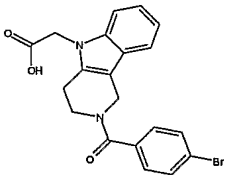
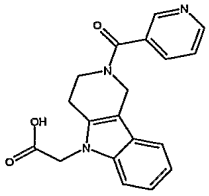
Ex	Structure	Name	Mol Formula Mol Weight	t_R [min] (LC)	MS Data *m/z* $[M+H]^+$
27		(2-diphenylacetyl-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetic acid	$C_{27}H_{24}N_2O_3$ 424.50	2.27 (LC-1)	425.17
28		(2-hexanoyl-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetic acid	$C_{19}H_{24}N_2O_3$ 328.41	2.10 (LC-1)	329.25
29		[2-(3-chloro-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid	$C_{20}H_{17}N_2O_3Cl$ 368.82	2.08 (LC-1)	369.12
30		[2-(4-bromo-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid	$C_{20}H_{17}N_2O_3Br$ 413.27	2.11 (LC-1)	415.05
31		[2-(pyridine-3-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid	$C_{19}H_{17}N_3O_3$ 335.36	1.62 (LC-1)	336.25

Table 2

Example 32: (2-Benzoyl-8-methoxy-1,2,3,4-tetrahydro-pyrido[4,3-*b*]-5-yl)-acetic acid

The title compound is obtained using conditions for the hydrolysis of ethyl (8-methoxy-2-phenylcarbamoyl-1, 2, 3, 4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetate analogous to Example 1: t_R (LC-1) 1.92; ESI-MS (positive ion): *m/z* 364.23 $[M]^+$ (calcd 364.39 for $C_{21}H_{20}N_2O_4$).

32a) 8-Methoxy-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole

A suspension of 4-piperidone monohydrate hydrochloride (1.0 g, 6.5 mmol) and 4-methoxyphenylhydrazine hydrochloride (1.14 g, 6.5 mmol) in ethanol (17 ml) is kept stirring at reflux overnight. The resulting solid is filtered off and washed with diethyl ether to afford crude sub-title compound, which is used without further purification: t_R (LC-1) 0.38; ESI-MS (positive ion): *m/z* 203.19 $[M+H]^+$ (calcd 202.25 for $C_{12}H_{14}N_2O$).

32b) 8-Methoxy-1,3,4,5-tetrahydro-pyrido[4,3-*b*]indole-2-carboxylic acid phenylamide

The subtitle compound is prepared using **Method B** as described for Example 6, substituting 8-methoxy-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-b]indole for Intermediate 1: t_R (LC-1) 2.03; ESI-MS (positive ion): *m/z* 307.21 $[M+H]^+$ (calcd 306.36 for $C_{19}H_{18}N_2O_2$).

32c) Ethyl (8-methoxy-2-phenylcarbamoyl-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetate

The subtitle compound is prepared according to Step 1c) in the procedure described for the synthesis of Intermediate 1, substituting 8-methoxy-1,3,4,5-tetrahydro-pyrido[4,3-*b*]indole-2-carboxylic acid phenylamide for 2-tert.-butoxycarbonyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indole: t_R (LC-1) 2.21 min; ESI-MS (positive ion): *m/z* 393.32 $[M+H]^+$ (calcd 392.17 for $C_{23}H_{24}N_2O_4$).

Examples 33-36 of the following Table 3 are prepared using a procedure analogous to that described for Example 32, substituting the appropriate phenylhydrazine for 4-methoxyphenylhydrazine.

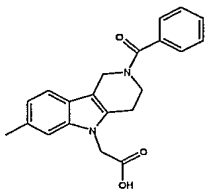
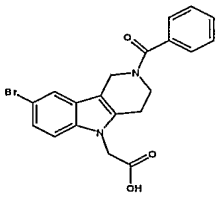
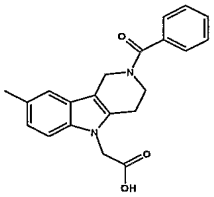
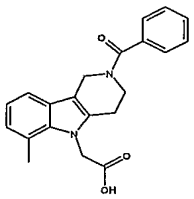
Ex.	Structure	Name	Mol Formula Mol Weight	t_R [min] (LC)	MS Data *m/z* $[M+H]^+$
33		(2-benzoyl-7-methyl-1,2,3,4-tetrahydro-pyrido[4,3-*b*]-5-yl)-acetic acid	$C_{21}H_{20}N_2O_3$ 348.40	2.03 (LC-1)	349.24
34		(2-benzoyl-8-bromo-1,2,3,4-tetrahydro-pyrido[4,3-*b*]-5-yl)-acetic acid	$C_{20}H_{17}BrN_2O_3$ 413.26	2.11 (LC-1)	413.13
35		(2-benzoyl-8-methyl-1,2,3,4-tetrahydro-pyrido[4,3-*b*]-5-yl)-acetic acid	$C_{21}H_{20}N_2O_3$ 348.40	2.05 (LC-1)	349.18
36		(2-benzoyl-6-methyl-1,2,3,4-tetrahydro-pyrido[4,3-*b*]-5-yl)-acetic acid	$C_{21}H_{20}N_2O_3$ 348.40	2.01 (LC-1)	349.24

Table 3

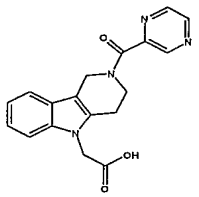
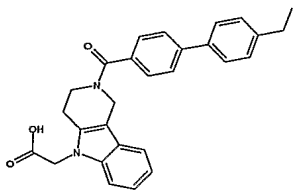
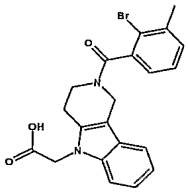
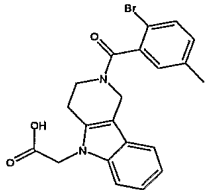
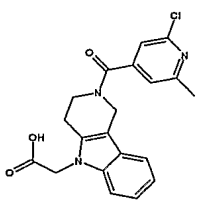
Example 37: [2-(2-Cyclohexyl-2-phenyl-acetyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid (Method C)

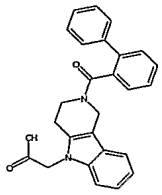
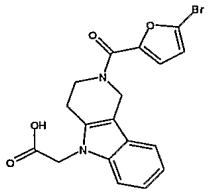
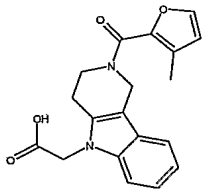
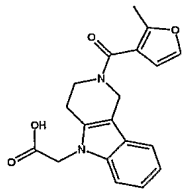
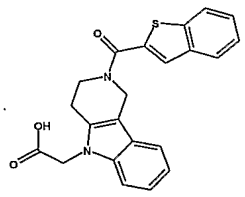
Step a): To a stirred solution of Intermediate 1 (25 mg, 0.085 mmol), cyclohexyl-phenylacetic acid (27.7 mg, 0.127 mmol) and DIEA (73 µl, 0.424 mmol) in dichloromethane (1 ml) is added $POCl_3$ (9 µl, 0.093 mmol). The resulting yellow reaction

mixture is stirred at rt overnight, then saturated aqueous $NaHCO_3$ solution (2 ml) is added. The organic layer is separated and washed with water (2 ml). Evaporation of the solvent gave a crude that is purified by silica gel column chromatography (hexane/ EtOAc 3:1) affording ethyl [2-(2-cyclohexyl-2-phenyl-acetyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetate as a white solid (29 mg) in 74% yield: t_R (LC-2) 2.74 min; ESI-MS (positive ion): *m/z* 459.25 $[M+H]^+$ (calcd 458.59 for $C_{29}H_{34}N_2O_3$).

Step b): The title compound is obtained using conditions for the hydrolysis of the above ester analogous to Example 1: t_R (LC-2) 2.47 min; ESI-MS (positive ion): *m/z* 431.22 $[M+H]^+$ (calcd 430.55 for $C_{27}H_{30}N_2O_3$).

Examples 38-52 of the following Table 4 are prepared using a procedure analogous to that described for Example 44, substituting the appropriate Intermediate for Intermediate 1 and substituting the appropriate acid for cyclohexylphenylacetic acid.

Ex.	Structure	Name	Mol Formula Mol Weight	t_R [min] ((LC)	MS Data *m/z* $[M+H]^+$
38		[2-(pyrazine-2-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid	$C_{18}H_{16}N_4O_3$ 336.35	1.80 (LC-1)	337.14
39		[2-(4'-ethyl-biphenyl-4-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid	$C_{28}H_{26}N_2O_3$ 438.53	2.50 (LC-1)	439.18
40		[2-(2-bromo-3-methyl-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid	$C_{21}H_{19}N_2O_3Br$ 427.30	2.15 (LC-1)	429.05
41		[2-(2-bromo-5-methyl-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid	$C_{21}H_{19}N_2O_3Br$ 427.30	2.17 (LC-1)	429.05
42		[2-(2-chloro-6-methyl-pyridine-4-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid	$C_{20}H_{18}N_3O_3Cl$ 383.83	2.00 (LC-1)	384.08

Ex.	Structure	Name	Mol Formula Mol Weight	t_R [min] ((LC)	MS Data *m/z* $[M+H]^+$
43		[2-(biphenyl-2-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid	$C_{26}H_{22}N_2O_3$ 410.47	2.23 (LC-1)	411.15
44		[2-(5-bromo-furan-2-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid	$C_{18}H_{15}N_2O_4Br$ 403.23	2.10 (LC-1)	403.00
45		[2-(3-methyl-furan-2-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid	$C_{19}H_{18}N_2O_4$ 338.36	2.01 (LC-1)	339.12
46		[2-(2-methyl-furan-3-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid	$C_{19}H_{18}N_2O_4$ 338.36	1.97 (LC-1)	339.18
47		[2-(benzo[*b*]thiophene-2-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid	$C_{22}H_{18}N_2O_3S$ 390.46	2.23 (LC-1)	391.09

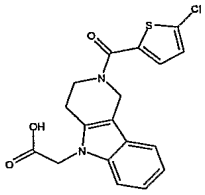
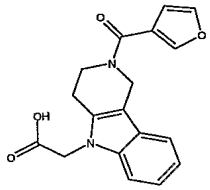
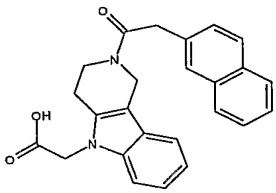
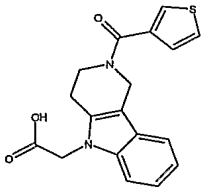
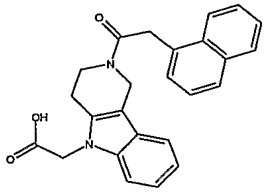
Ex	Structures	Name	Mol Formula Mol Weight	t_R [min] ((LC)	MS Data *m/z* $[M+H]^+$
48		[2-(5-chloro-thiophene-2-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid	$C_{18}H_{15}N_2O_3ClS$ 374.85	2.20 (LC-1)	375.04
49		[2-(furan-3-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid	$C_{18}H_{16}N_2O_4$ 324.34	1.89 (LC-1)	325.17
50		[2-(2-naphthalen-2-yl-acetyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid	$C_{25}H_{22}N_2O_3$ 398.46	2.23 (LC-1)	399.18
51		[2-(thiophene-3-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid	$C_{18}H_{16}N_2O_3S$ 340.40	1.96 (LC-1)	341.09
52		[2-(2-naphthalen-1-yl-acetyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid	$C_{25}H_{22}N_2O_3$ 398.46	2.24 (LC-1)	399.18

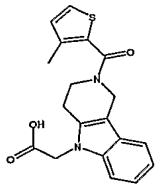
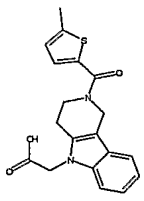
Table 4

Example 53: [2-(2-Ethoxy-naphthalene-1-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid (Method D)

Step a): To a solution of 2-ethoxynaphthoic acid (22 mg, 0.1mmol), N',N',N',N'-tetramethyl-O-(7-azabenzotriazole-1-yl)-uronium-hexafluorophosphate (38 mg, 0.1mmol) and DIEA (51 µl, 0.3 mmol) in THF/DMF (4:1, 1 ml) is added Intermediate 1 (29 mg, 0.1 mmol) in one portion and the reaction mixture is stirred at rt overnight. Then, the solvent is evaporated and the residue purified by silica gel column chromatography (6% MeOH in CH_2Cl_2, / aqueous NH_4OH 9:1) affording ethyl [2-(2-ethoxy-naphthalene-1-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetate (43 mg) as a glassy brown solid in 93% yield.

Step b): The title compound is obtained using conditions for the hydrolysis of the above ester analogous to Example 1: t_R (LC-2) 2.49 min; ESI-MS (positive ion): *m/z* 429.24 $[M+H]^+$ (calcd 428.48 for $C_{26}H_{24}N_2O_4$).

Examples 54-56 of the following Table 5 are prepared using a procedure analogous to that described for Example 53, substituting the appropriate acid for 2-ethoxynaphthoic acid.

Ex.	Structure	Name	Mol Formula Mol Weight	t_R [min] (LC)	MS Data *m/z* $[M+H]^+$
54		[2-(3-Methyl-thiophene-2-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid	$C_{19}H_{18}N_2O_3S$ 354.43	2.33 (LC-2)	355.23
55		[2-(5-Methyl-thiophene-2-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid	$C_{19}H_{18}N_2O_3S$ 354.43	2.38 (LC-2)	355.23

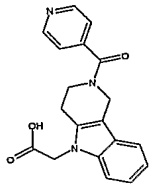
Ex.	Structure	Name	Mol Formula Mol Weight	t_R [min] (LC)	MS Data *m/z* $[M+H]^+$
56		[2-(Pyridine-4-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid	$C_{19}H_{17}N_3O_3$ 335.36	1.90 (LC-2)	336.25

Table 5

Example 57: (2-Phenylcarbamoyl-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetic acid (Method E)

Step a): To a stirred solution of Intermediate 1 (20 mg, 0.068 mmol) and DIEA (35 µl, 0.20 mmol) in dichloromethane (1 ml) is added phenyl isocyanate (8.2 µl, 0.075 mmol). The reaction mixture is kept stirring at rt for 1 h, then 1N HCl (2 ml) was added. The aqueous layer is extracted twice with dichloromethane. The organic layers are combined and the solvent is evaporated to give crude ethyl (2-phenylcarbamoyl-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetic acid: t_R (LC-2) 2.23 min; ESI-MS (positive ion): *m/z* 400.39 $[M+Na]^+$ (calcd 377.44 for $C_{22}H_{23}N_3O_3$).

Step b): The title compound is obtained using conditions for the hydrolysis of the above crude analogous to Example 1: t_R (LC-2) 1.95 min; ESI-MS (positive ion): *m/z* 350.26 $[M+H]^+$ (calcd 349.39 for $C_{20}H_{19}N_3O_3$).

Example 58: (2-Ethylcarbamoyl-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetic acid

The title compound is prepared using a procedure analogous to Example 57, substituting ethyl isocyanate for phenyl isocyanate: t_R (LC-2) 1.68 min; ESI-MS (positive ion): *m/z* 302.24 $[M+H]^+$ (calcd 301.35 for $C_{16}H_{19}N_3O_3$).

Example 59: (2-Phenethyl-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetate, sodium salt (Method F)

Step a): To a stirred solution of Intermediate 1 (50 mg, 0.17 mmol) and DIEA (73 µl, 0.42 mmol) in acetonitrile (1 ml) is added (2-bromo-ethyl)-benzene (26 µl, 0.19 mmol). The reaction mixture is stirred at rt overnight. The solvent is removed under reduced pressure and the crude product is purified by silica gel column chromatography (hexane/ EtOAc 3:1, 1% NEt_3), affording pure ethyl (2-phenethyl-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-acetate (37 mg) in 60% yield: t_R (LC-2) 1.69 min; ESI-MS (pos. ion): *m/z* 363.26 $[M+H]^+$ (calcd 362.46 for $C_{23}H_{26}N_2O_2$).

Step b): A stirred solution of the above ester in THF (1 ml) was treated with 0.2 N aqueous NaOH (0.51 ml, 0.10 mmol) at rt for 15 min. The yellow solution is diluted with 0.5 ml of water and washed twice with diethyl ether (2 ml each). The aqueous phase is concentrated and the precipitate filtered off, affording pure title compound (29 mg) in 79% yield: t_R (LC-2) 1.55 min; ESI-MS (pos. ion): *m/z* 335.36 $[M+H]^+$ (calcd 334.41 for $C_{21}H_{22}N_2O_2$).

Example 60: [2-(3-Phenyl-propyl)-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl]-acetate, sodium salt

The title compound is prepared using a procedure analogous to Example 59, substituting (3-bromo-propyl)-benzene (2-bromo-ethyl)-benzene: t_R (LC-2) 1.61 min; ESI-MS (positive ion): *m/z* 349.37 $[M+H]^+$ (calcd 348.44 for $C_{22}H_{24}N_2O_2$).

Biological assay:

Preparation of CRTH2 membranes and radioligand binding assay:

Preparation of the membranes and radioligand binding assays are performed according to known procedures, e.g. Sawyer N. et al. (*Br. J. Pharmacol.*, 2002, **137**, 1163-1172). A clonal HEK 293 cell line, expressing high level of recombinant hCRTH2 receptor, is selected for the preparation of membranes. Cells are detached from culture plates in 5 ml

buffer A per plate (5 mM Tris, 1 mM $MgCl_2x6\ H_2O$, 0.1 mM PMSF, 0.1 mM phenanthroline) using a police rubber and transferred into centrifugation tubes and frozen at –80°C. After thawing, the cells are centrifuged at 500 g for 5 min and then resuspended in buffer A. Cells are then fragmented by homogenization with a Polytron homogenizer for 30 s. The membrane fragments are centrifuged at 3000 g for 40 min and resuspended in membranes in buffer B (50 mM Tris, 25 mM $MgCl_2$, 250 mM saccharose, pH 7.4) and aliquots are stored frozen.

Binding assay is performed in a total volume of 250 µl. In each well, 75 µl buffer C (50 mM Tris, 100 mM NaCl, 1 mM EDTA, 0.1% BSA (protease free), 0.01 % NaN_3, pH 7.4) was mixed with 50 µl $\{^3H\}$-PGD_2 (at 2.5 nM (220.000 dpm per well) from Amersham, TRK734), 100 µl CRTH2 membranes to give 80 µg per well and 25 µl of test compound in buffer C containing 1% DMSO. For unspecific binding, PGD2 is added to the reaction mixture at 1 µM final concentration. This binding assay mix is incubated at rt for 90 min and then filtered through a GF/C filter plate. The filter is washed three times with ice cold binding buffer. Then, 40 µl per well Microscint-40 (Packard) are added and the bound radioactivity is quantified by means of Topcount (Packard).

Test for antagonist binding to the CRTH2 receptor:

Compounds of Formula (I) displayed IC_{50} values of less than 10 µM, as exemplified in the following Table 6.

Name	Binding CRTH2 IC_{50} [µM]
[2-(Naphthalene-1-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid	0.002
[2-(3-Chloro-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl] acetic acid	0.007
[2-(2-Bromo-3-methyl-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid	0.009
[2-(4'-Ethyl-biphenyl-4-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid	0.009

Table 6

Intracellular calcium mobilization assay (FLIPR):

Cells (HEK-293), stably expressing the $hCRTH_2$ receptor under the control of the cytomegalovirus promotor from a single insertion of the expression vector pcDNA5 (Invitrogen), are grown to confluency in DMEM (low glucose, Gibco) medium supplemented with 10% fetal calf serum (both Bioconcept, Switzerland) under standard mammalian cell culture conditions (37°C in a humidified atmosphere of 5% CO_2). Cells are detached from culture dishes using a dissociation buffer (0.02% EDTA in PBS, Gibco) for 1 min, and collected by centrifugation at 200g at rt for 5 min in assay buffer (equal parts of Hank's BSS (HBSS, Bioconcept) and DMEM (low glucose, without phenol red, Gibco)). After incubation for 45 min (37°C and 5% CO_2) in the presence of 1 µM Fluo-4 and 0.04% Pluronic F-127 (both Molecular Probes), 20mM HEPES (Gibco) in assay buffer, the cells

are washed with and resuspended in assay buffer, then seeded onto 384-well FLIPR assay plates (Greiner) at 50,000 cells in 66µl per well), and sedimented by centrifugation.

Stock solutions of test compounds are made up at a concentration of 10 mM in DMSO, and serially diluted in assay buffer to concentrations required for inhibition dose response curves. Prostaglandin D_2 (Biomol, Plymouth Meeting, PA) is used as an agonist.

A FLIPR384 instrument (Molecular Devices) is operated according to the manufacturer's standard instructions, adding 4 µl of test compound dissolved at 10mM in DMSO and diluted prior to the experiment in assay buffer to obtain the desired final concentration. 10µl of 80 nM prostaglandin D_2 (Biomol, Plymouth Meeting, PA) in assay buffer, supplemented with 0.8% bovine serum albumin (fatty acid content <0.02%, Sigma), is then added to obtain a final concentration of 10nM and 0.1%, respectively. Changes in fluorescence are monitored before and after the addition of test compounds at λ_{ex}=488 nm and λ_{em}=540 nm. Emission peak values above base level after prostaglandin D_2 addition are exported after base line subtraction. Values are normalized to high-level control (no test compound added) after subtraction of base line value (no prostaglandin D_2 added). The program XLlfit 3.0 (IDBS) is used to fit the data to a single site dose response curve of the equation (A+((B-A)/(1+((C/x)^D)))) and to calculate the IC_{50} values.

Antagonist analysis

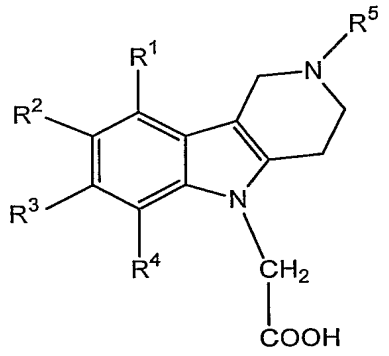
Compounds of Formula I antagonize prostaglandin D2 mediated hCRTH2 receptor activity with an IC_{50} less than 10 μM as exemplified in the following Table 7.

Name	**FLIPR CRTH2 IC_{50} [μM]**
[2-(Naphthalene-1-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid	0.028
(2-Benzoyl-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetic acid	0.076
[2-(3-Chloro-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl] acetic acid	0.078
[2-(4-Bromo-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl] acetic acid	0.083
[2-(Furan-2-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl] acetic acid	0.088

Table 7

Claims:

1. Tetrahydropyridoindole derivatives of the general Formula (I)



(I)

wherein

R^1, R^2, R^3 and R^4 independently represent hydrogen, C_1-C_5 alkyl, C_1-C_5 alkoxy, halogen, nitro, cyano or formyl;

R^5 represents alkyl carbonyl, alkenyl carbonyl, alkoxycarbonyl, alkyl, alkylcarbamoyl, aryl-C_1-C_5-alkyl, aryl carbonyl, aryl-C_1-C_5-alkyl carbonyl, aryl C_1-C_5-alkoxycarbonyl, arylcarbamoyl, cycloalkylcarbonyl, cycloalkyl-C_1-C_5-alkyl carbonyl, cycloalkyl-C_1-C_5-alkoxy carbonyl, heteroaryl C_1-C_5-alkyl, heteroaryl carbonyl, heteroaryl-C_1-C_5-alkyl carbonyl or heteroaryl C_1-C_5-alkoxycarbonyl; with the proviso that when R^1, R^2, R^3 and R^4 represent hydrogen, R^5 is not an ethoxy-carbonyl group or a tert.-butoxycarbonyl group;

and optically pure enantiomers, mixtures of enantiomers, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixture of diastereoisomeric racemates, or meso forms and pharmaceutically acceptable salts thereof.

2. Tetrahydropyridoindole derivatives according to claim 1 wherein R^1, R^2, R^3 and R^4 represent hydrogen.

3. Tetrahydropyridoindole derivatives according to claim 1 wherein R^1, R^2, R^3 and R^4 represent C_1-C_5 alkyl, C_1-C_3 alkoxy, halogen, nitro, cyano or formyl.

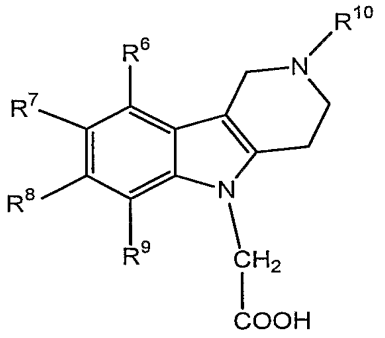
4. Tetrahydropyridoindole derivatives according to claim 3 wherein one or two substituents selected from R^1, R^2, R^3 and R^4 represent methyl, trifluoromethyl, methoxy, fluoro, chloro or bromo.

5. Tetrahydropyridoindole derivatives according to claim 1 wherein R^5 is selected from the group consisting of 2-cyclohexyl-2-phenyl-acetyl, 2-naphthalen-1-yl-acetyl, 2-naphthalen-2-yl-acetyl, 3-cyclopentyl-propionyl, 3-phenyl-propionyl, acetyl, diphenylacetyl, hexanoyl, preferably (E)-but-2-enoyl, 9H-fluoren-9-ylmethoxycarbonyl, benzyloxycarbonyl, butoxycarbonyl, 3-phenyl-propyl, phenethyl, phenylacetyl, ethylcarbamoyl, 2-bromo-3-methyl-benzoyl, 2-bromo-5-methyl-benzoyl, 2-methoxy-benzoyl, 3,4,5-trimethoxy-benzoyl, 3,5-bis-trifluoromethyl-benzoyl, 3,5-dimethoxy-benzoyl, 3-chloro-benzoyl, 4-bromo-benzoyl, 4-chloro-benzoyl, 4-methoxy-benzoyl, 4-tert.-butyl-benzoyl, 4-trifluoromethoxy-benzoyl, 4-trifluoromethyl-benzoyl, or benzoyl; phenylcarbamoyl, 4'-ethyl-biphenyl-4-carbonyl, biphenyl-2-carbonyl, biphenyl-4-carbonyl, 2-ethoxy-naphthalene-1-carbonyl or naphthalene-1-carbonyl, cyclohexane-carbonyl, cyclopropane-carbonyl, pyridine-3-carbonyl, 2-chloro-6-methyl-pyridine-4-carbonyl, pyridine-4-carbonyl, furan-2-carbonyl, furan-3-carbonyl, 2-methyl-furan-3-carbonyl, 3-methyl-furan-2-carbonyl, 5-bromo-furan-2-carbonyl, pyrazine-2-carbonyl, benzo[b]thiophene-2-carbonyl, 5-chloro-thiophene-2-carbonyl, 3-methyl-thiophene-2-carbonyl, 5-methyl-thiophene-2-carbonyl, thiophene-2-carbonyl or thiophene-3-carbonyl.

6. Tetrahydropyridoindole derivatives according to claim 1 wherein R^1, R^2, R^3 and R^4 represent hydrogen, R^5 represents a C_1-C_5 alkoxycarbonyl group, an aryl-C_1-C_5-alkyl carbonyl group, an aryl carbonyl group or a heteroaryl carbonyl group.

7. Tetrahydropyridoindole derivatives according to claim 6 wherein R^1, R^2, R^3 and R^4 represent H, R^5 represents a C_1-C_5 alkoxycarbonyl group, a phenyl C_1-C_5 alkyl carbonyl group, a naphthalene-1-carbonyl group or a thiophene-2-carbonyl group.

8. Tetrahydropyridoindole derivatives of the general Formula (II)



(II)

wherein

R^6, R^7, R^8 and R^9 independently represent hydrogen, C_1-C_5 alkyl, C_1-C_3 alkoxy or halogen;

R^{10} represents alkyl-carbonyl, alkoxy-carbonyl, alkenyl-carbonyl, C_3-C_6-cycloalkyl, C_3-C_6 cycloalkyl-carbonyl, C_3-C_6 cycloalkoxy-carbonyl, C_3-C_6 cycloalkyl-C_1-C_3-alkyl carbonyl, C_3-C_6 cycloalkyl-C_1-C_3-alkoxy carbonyl, phenyl-carbonyl, phenyl-C_1-C_3 alkyl carbonyl or phenyloxy-carbonyl whereby the phenyl group may be independently mono-, di- or tri-substituted with C_1-C_4 alkyl, C_1-C_3 alkoxy, halogen, trifluoromethyl or trifluoromethoxy, or mono-substituted with a phenyl group which in turn may be substituted with a C_1-C_3 alkyl or C_1-C_3-alkoxy group, naphtyl-carbonyl, fluorenyl-C_1-C_3-alkoxy-carbonyl, five- or six-membered heteroaryl-carbonyl groups containing one to three heteroatoms consisting independently of oxygen, nitrogen or sulfur and which groups may be independently substituted with

one or two C_1-C_3-alkyl, C_1-C_3-alkoxy, halogen or trifluoromethyl;
with the proviso that when R^6, R^7, R^8 and R^9 represent hydrogen, R^{10} is not an ethoxy-carbonyl group or a tert.-butoxycarbonyl group;

and optically pure enantiomers, mixtures of enantiomers, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixture of diastereoisomeric racemates, or meso forms and pharmaceutically acceptable salts thereof.

9. A tetrahydropyridoindole derivative according to any of the preceding claims selected from the group consisting of:

(2-benzyloxycarbonyl-1, 2, 3,4-tetrahydro-pyrido[4,3-b]indol-5-yl)-acetic acid;

(2-butoxycarbonyl-1, 2, 3, 4-tetrahydro-pyrido[4,3-b]indol-5-yl)-acetic acid;

(2-9H-fluoren-9-ylmethoxycarbonyl-1, 2, 3, 4-tetrahydro-pyrido[4,3-b]indol-5-yl)-acetic acid;

(2-acetyl-1, 2, 3, 4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetic acid;

(2-phenylacetyl-1, 2, 3, 4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetic acid;

(2-benzoyl-1, 2, 3, 4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetic acid;

[2-(3,4,5-trimethoxy-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

(2-cyclohexanecarbonyl-1, 2, 3, 4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetic acid;

[2-(4-methoxy-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(thiophene-2-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(furan-2-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

(2-cyclopropanecarbonyl-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetic acid;

[2-(naphthalene-1-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(2-methoxy-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(4-trifluoromethyl-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(3,5-bis-trifluoromethyl-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(3-cyclopentyl-propionyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(3-phenyl-propionyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(biphenyl-4-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(4-tert.-butyl-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(4-trifluoromethoxy-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-((E)-but-2-enoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(4-chloro-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(3,5-dimethoxy-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

(2-diphenylacetyl-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetic acid;

(2-hexanoyl-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetic acid;

[2-(3-chloro-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(4-bromo-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(pyridine-3-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

(2-benzoyl-8-methoxy-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetic acid;

(2-benzoyl-7-methyl-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetic acid;

(2-benzoyl-8-bromo-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetic acid;

(2-benzoyl-8-methyl-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetic acid;

(2-benzoyl-6-methyl-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetic acid;

[2-(pyrazine-2-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(2-bromo-3-methyl-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(4'-ethyl-biphenyl-4-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(2-bromo-5-methyl-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(2-chloro-6-methyl-pyridine-4-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(biphenyl-2-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(5-bromo-furan-2-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(3-methyl-furan-2-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(2-methyl-furan-3-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(benzo[*b*]thiophene-2-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(5-chloro-thiophene-2-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(furan-3-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(2-naphthalen-2-yl-acetyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(thiophene-3-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(2-naphthalen-1-yl-acetyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

rac. [2-(2-cyclohexyl-2-phenyl-acetyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

(2-phenylcarbamoyl-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetic acid;

(2-ethylcarbamoyl-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetic acid;

sodium (2-phenethyl-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetate;

sodium [2-(3-phenyl-propyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetate;

[2-(2-ethoxy-naphthalene-1-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-b]indol-5-yl]-acetic acid;

[2-(3-methyl-thiophene-2-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(5-methyl-thiophene-2-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(pyridine-4-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid.

10. Tetrahydropyridoindole derivative according to claim 9 selected from the group consisting of:

[[2-(naphthalene-1-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(3-chloro-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(4'-ethyl-biphenyl-4-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

[2-(2-bromo-3-methyl-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl]-acetic acid;

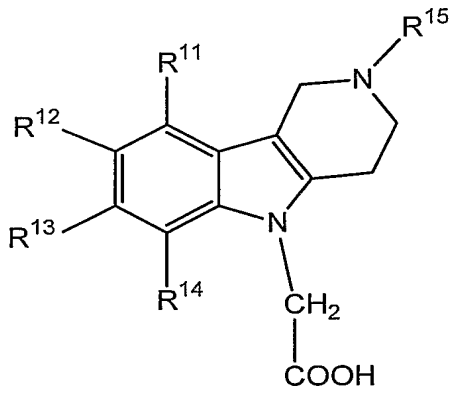
(2-benzoyl-8-bromo-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetic acid;

(2-benzoyl-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl)-acetic acid;

[2-(4-bromo-benzoyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl] acetic acid;

[2-(furan-2-carbonyl)-1,2,3,4-tetrahydro-pyrido[4,3-*b*]indol-5-yl] acetic acid.

11. Pharmaceutical composition containing at least one tetrahydropyridoindole derivative of the following general Formula (III):



(III)

wherein

R^{11}, R^{12}, R^{13} and R^{14} independently represent hydrogen, C_1-C_5 alkyl, C_1-C_5 alkoxy, halogen, nitro, cyano or formyl;

R^{15} represents alkyl carbonyl, alkenyl carbonyl, alkoxycarbonyl, alkyl, alkylcarbamoyl, aryl-C_1-C_5-alkyl, aryl carbonyl, aryl-C_1-C_5-alkyl carbonyl, aryl C_1-C_5-alkoxycarbonyl, arylcarbamoyl, cycloalkylcarbonyl, cycloalkyl-C_1-C_5-alkyl carbonyl, cycloalkyl-C_1-C_5-alkoxy carbonyl, heteroaryl C_1-C_5-alkyl, heteroaryl carbonyl, heteroaryl-C_1-C_5-alkyl carbonyl or heteroaryl C_1-C_5-alkoxycarbonyl;

and optically pure enantiomers, mixtures of enantiomers, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixture of diastereoisomeric racemates, or meso forms, pharmaceutically acceptable salts thereof and inert carrier materials or adjuvants.

12. Use of a pharmaceutical composition according to claim 11 for the prevention or treatment of diseases selected in the group consisting of both chronic and acute allergic/immune disorders such as allergic asthma, rhinitis, chronic obstructive pulmonary disease, dermatitis, inflammatory bowel disease, rheumatoid arthritis, allergic nephritis, conjunctivitis, atopic dermatitis, bronchial asthma, food allergy, systemic mast cell disorders, anaphylactic shock, urticaria, eczema, itching, inflammation, ischemia-reperfusion injury, cerebrovascular disorders, pleuritis, ulcerative colitis, eosinophil-related diseases, such as Churg-Strauss syndrome and sinusitis, basophil-related diseases, such as basophilic leukemia and basophilic leukocytosis.

13. A method for the treatment or prophylaxis of disease states mediated by CRTH2 comprising the administration to the patient a pharmaceutically active amount of a tetrahydropyridoindole derivative according to Formula (III).

14. A method according to claim 13 wherein said amount is comprised between 1 mg and 1000 mg per day.

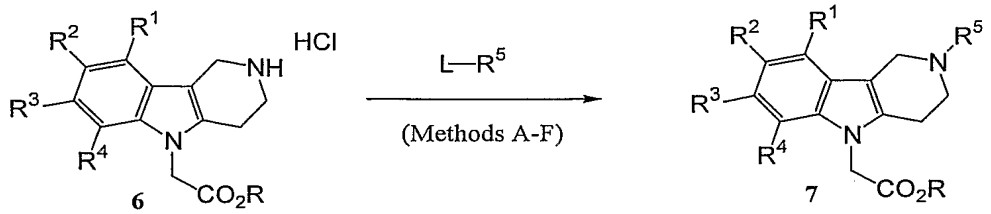
15. A method according to claim 14 wherein said amount is comprised between 2 mg and 500 mg per day.

16. A method according to claim 15 wherein said amount is comprised between 5 mg and 200 mg per day.

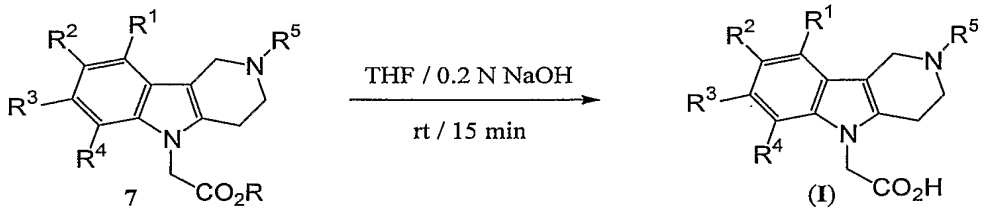
17. A process for the preparation of a pharmaceutical composition according to claim 11, characterized by mixing one or more active ingredients according to general Formula (III) with inert excipients in a manner known *per se*.

18. A process for the preparation of a tetrahydropyridoindole derivative of Formula (I) according to any of claims 1 to 10 comprising the two following steps a) and b):

Step a)

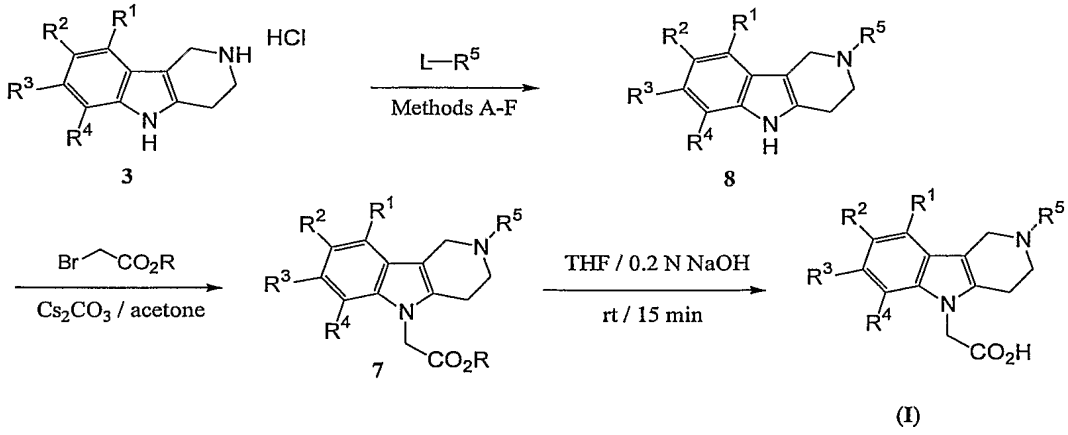


Step b)



wherein R is an alkyl group, L is a leaving group, R^1, R^2, R^3, R^4 and R^5 are as defined in claim 1.

19. A process for the preparation of a tetrahydropyridoindole derivative of Formula (I) according to any of claims 1 to 10 comprising the following steps



wherein R is an alkyl group, L is a leaving group, R^1, R^2, R^3, R^4 and R^5 are as defined in claim 1.

Abstract

The invention relates to tetrahydropyridoindole derivatives and their use as active ingredients in the preparation of pharmaceutical compositions. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more of those compounds and methods of treatment comprising administration of said compounds.